REMARKS

Claims 1-2, and 4-28 are pending in the application. Claims 11-25 are withdrawn from consideration as being drawn to a non-elected invention. Claim 26 has been canceled without prejudice or disclaimer. Claims 1, 2, 27 and 28 have been amended to better clarify what Applicants believe to be the invention. New claim 29 has been added for consideration. Support for the claim amendments can be found throughout the specification, but particularly in paragraphs [0021] on pages 7-8; [0026] on pages 9-10; [0027] on page 10 ; [0030] on page 11; [0031] on pages 11-12; [0032] on page 12; [0065] on pages 21-22; [0067] on page 23; [0068] on page 23; [0091] on page 30; [0092] on pages 30-31; [0097] on page 32; [0099] on page 33; [0117] on page 36; [0118] on pages 36-37; [0122] on page 38; [0141] on page 43; [0143] on page 44; [0145] on page 44; [0148] on page 44; [0152] on page 45; [0159] on page 46; [0161] on page 46; [0190] on page 50; and [0198] on page 51 and in the Examples. No new matter has been entered by way of this amendment. Accordingly, if new claim 29 is entered by way of this amendment, claims 1-2, 4-10 and 27 through 29 are currently under consideration. Reconsideration of this application is respectfully requested.

Applicants' representatives would like to express their sincere appreciation for the courteous and constructive telephonic interview held with Examiners Susan Beth McCormick-Ewoldt and Christopher Tate on June 28, 2006, as related to the claims under consideration. As noted in that telephone conversation, Applicants provided a summary of the differences between the cited references and the present invention. The Examiners suggested modifying the claims to be in product by process format. Applicants' representative proposed particular claim amendments related to the fact that the currently claimed extract was present in a buffered aqueous solution, which was not taught by the cited references. Examiner Tate noted that this type of amendment would help in differentiating the compositions of the present invention over the cited art, providing there was support for such amendment in the specification. Examiner Tate also recommended including the particular indications for which the present compositions would be used. He also asked that the extract of claim 1 be limited to that from Nigella sativa and that the concentration be maintained as currently claimed, that is, no less than 20% weight per volume. Examiner Tate also asked that the same changes be made to the other relevant claims. Applicants and Applicants' representative thanked the Examiners for their constructive

input and agreed to prepare such amendment for submission.

Rejection under 35 U.S.C. §102

The Examiner has rejected claims 1, 2, 4-10, and 26-28 under 35 U.S.C. §102(e) as being anticipated by Kandil et al. (U.S. 2002/0132019).

The Examiner's Position

The Examiner alleges that Kandil (US2002/0132019) expressly teaches using *Nigella sativa* in a pharmaceutical composition in an amount of about .1 to about 25% by weight. In addition, the Examiner alleges that Kandil discloses the composition can be used in tablets, capsules, liquid, suspensions, nasal forms, suppositories, topical administration and a transdermal patch and therefore, the teaching of Kandil, meet the limitations of claims 1, 2 and 26 and thus anticipates the claimed invention.

Applicants' Invention as Currently Claimed

The present invention, as currently amended and claimed, is directed to a pharmaceutical composition for treating a hepatic disorder and/or for increasing the number of immune cells and platelets in a patient, consisting essentially of a therapeutically effective amount of **a buffered aqueous extract** of Nigella sativa, and a pharmaceutically acceptable carrier, wherein the extract of Nigella sativa is present in a concentration of not less than 20% weight per volume.
In another embodiment, the present invention is also drawn to a pharmaceutical composition for treating a hepatic disorder and/or for increasing the number of immune cells and platelets in a patient consisting essentially of a therapeutically effective amount of **a buffered aqueous extract** of Anemone hepatica and Nigella sativa, and a pharmaceutically acceptable carrier, wherein the extract of Nigella sativa is present in a concentration of not less than 20% weight per volume. The composition may be delivered in the form of a tablet, or capsule, or liquid suspension, or may be delivered intramuscularly, subcutaneously, intravenously, intranasally, topically, transdermally, or in the form of a suppository. The composition is effective for treating patients suffering from a hepatic disorder selected from the group consisting of chronic hepatitis, advanced/late stage hepatitis, hepatitis caused by hepatitis virus genotypes I, II, II or

IV, a hepatic disorder characterized by fibrosis and/or cirrhosis, a hepatic disorder resulting from an autoimmune disease and a hepatic disorder resulting from a drug treatment. Treating patients with the composition results in modification of disease activity, including but not limited to, a decrease in hepatitis viral load, and a decrease in liver enzymes alanine aminotransferase (ALT) levels and aspartate aminotransferase (AST) levels.

Claim Amendments and Arguments in Support of Patentability over Kandil

Applicants respectfully traverse the Examiner's rejection and assert that in order for a rejection under 35 U.S.C. §102 to be proper, the reference(s) must teach each and every element of the invention as claimed. Applicants assert that Kandil does not teach the compositions of the present invention as currently claimed.

Kandil teaches a composition comprising **a Nigella sativa L. sterol fraction in an amount of about 0.5 to about 25% by weight based on 100% by weight of the total composition**. More particularly, the composition taught by Kandil comprises sitosterol, campesterol, amyrin and stigmasterol. Vaginal and topical compositions comprising these sterol fractions are also taught by Kandil, as well as methods of treating or preventing a fungal or bacterial infection, inflammation, pain or an allergic reaction using these compositions **comprising a sterol fraction from Nigella sativa**.

It should be noted that Applicants' composition, as currently claimed, is a **buffered aqueous** extract of Nigella sativa present in a **concentration of not less than 20% weight per volume**, support for which is shown in the present application on page 23, paragraph [0068] and further on page 30, paragraphs [0091] and [0092].

Applicants respectfully draw the Examiner's attention to Figure 1 of the Kandil reference. As shown in the flow diagram, Kandil prepares the extract of Nigella sativa by crushing the seeds in a non-polar solvent, eg. petroleum ether or hexane, utilizes the lipid fraction (sterol fraction) and discards the non-polar solvent-insoluble components including proteins, carbohydrates, crude fiber and ash. Based on this, Applicants assert that the Kandil reference actually teaches away from the present invention. It appears that the active moiety of Kandil is hydrophobic in nature, since Kandil discards the proteins and carbohydrates, and retains the lipid soluble fraction. On the other hand, the compositions of the present invention

consist essentially of a polar extract of one of the plants of the invention in a **buffered aqueous solution**. Furthermore, as noted in the present application, Applicants do not prepare a lipid fraction eg. a sterol fraction, for use in the compositions of the present invention. More particularly, the claims as currently amended specifically teach a composition consisting essentially of a buffered aqueous extract of Nigella sativa in a concentration of not less than 20% weight per volume for treating hepatic disorders and for increasing the number of immune cells and platelets.

For example, Applicants have amended claim 1 to recite:

"A pharmaceutical composition for treating a hepatic disorder and/or for increasing the number of immune cells and platelets in a patient, consisting essentially of a therapeutically effective amount of ***a buffered aqueous extract*** *of Nigella sativa and a pharmaceutically acceptable carrier, wherein the extract of Nigella sativa is present in a concentration of not less than 20% weight per volume."*

Furthermore, claim 2 has been amended to recite:

"A pharmaceutical composition for treating a hepatic disorder and/or for increasing the number of immune cells and platelets in a patient consisting essentially of a therapeutically effective amount of ***a buffered aqueous extract*** *of Anemone hepatica and Nigella sativa, and a pharmaceutically acceptable carrier, wherein the extract of Nigella sativa is present in a concentration of not less than 20% weight per volume."*

Applicants submit that Kandil **does not teach or suggest** a composition for treating a hepatic disorder and/or for increasing the number of immune cells and platelets in a patient consisting essentially of a therapeutically effective amount of **a buffered aqueous extract of** Nigella sativa, and a pharmaceutically acceptable carrier, wherein the extract of Nigella sativa is present in a concentration of not less than 20% weight per volume.

In addition, Applicants further assert that Kandil **does not teach or suggest** a pharmaceutical composition for treating a hepatic disorder and/or for increasing the number of immune cells and platelets in a patient consisting essentially of a therapeutically effective amount of **a buffered aqueous extract of** Anemone hepatica and Nigella sativa and a pharmaceutically acceptable carrier, wherein the extract of Nigella sativa is present in a concentration of not less than 20% weight per volume.

Furthermore, claim 26 has been canceled, thus rendering the rejection under 35 U.S.C. §102 (e) moot. Applicants further assert that the amendments to claims 1 and 2, as noted above, also render the rejection of the claims under 35 U.S.C. §102(e) moot. That is, Applicants submit that based on the foregoing amendments to the claims, Kandil **does not teach or suggest** the compositions of the instant invention.

Withdrawal of the rejection under 35 U.S.C. §102(e) is respectfully requested.

Rejection under 35 U.S.C. §103 (a)

The Examiner has also rejected claims 1-2, 4-10 and 26-28 under 35 U.S.C. §103(a) as being unpatentable over Kandil (US2002/0132019) and Medenica (US 5, 653,981).

The Examiner's Position Regarding Kandil

As noted above, the Examiner alleges that Kandil (US2002/0132019) beneficially discloses using *Nigella sativa* in a pharmaceutical composition in an amount of about .1 to about 25% by weight. In addition, the Examiner alleges that Kandil discloses the composition can be used in tablets, capsules, liquid, suspensions, nasal forms, suppositories, topical administration and a transdermal patch.

Kandil does not disclose wherein the pharmaceutical composition is used for hepatitis. However, the Examiner notes that a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention in the prior art in order to patentably distinguish the claimed invention from the prior art.

The Examiner alleges that one of ordinary skill in the art would have been motivated and would have a reasonable expectation to use *Nigella sativa* in a pharmaceutical composition since it is clear from the Kandil reference that Nigella sativa is used in a pharmaceutical composition to treat fungal infections in an amount of about .1 to about 25% by weight and discloses the composition can be used in tablets, capsules, liquid, suspensions, nasal forms, suppositories, topical administration and a transdermal patch.

The Examiner's Position Regarding Medenica

The Examiner has maintained the rejection in light of Medenica. More particularly, the Examiner alleges as before that Medenica discloses an extract of *Nigella sativa* in a pharmaceutical composition which is effective to increase the immune function and help restore the immune competent cells (column 3, lines 38-42; column 4, lines 14-15). In addition, Medenica also discloses administration of the extract of *Nigella sativa* by itself with an appropriate excipient or carrier. It may be administered by such methods as intramuscular, intravenous, subcutaneous, capsules, tablets, suppositories or the like (column 5, lines 31-42).

Medenica does not disclose wherein the pharmaceutical composition is used for hepatitis. However, the Examiner again notes that a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art.

The Examiner alleges that one of ordinary skill in the art would have been motivated and would have a reasonable expectation to use *Nigella sativa* by itself with an appropriate excipient or carrier in a pharmaceutical composition. It may be administered by such methods as intramuscular, intravenous, subcutaneous, capsules, tablets suppositories or the like.

With regards to the declarations submitted on April 6, 2006, the Examiner has considered the results. However, the Examiner notes that these results were not persuasive or unexpected because the Examiner alleges that the prior art teaches the same composition as claimed even though the intended use of the composition is different.

The Examiner fails to set forth a proper *prima facie* case of obviousness

As noted above, Applicants assert that a rejection under 35 U.S.C. §103 is proper only when a prior art reference alone or in combination with a second prior art reference renders the invention obvious. Applicants further assert that a rejection based upon a combination of references is not proper unless the following three criteria are met: 1) the references in combination teach every single element of the invention as claimed; 2) there must be some suggestion or motivation in the prior art to combine the references to reach the invention as claimed; and 3) there must be a reasonable expectation of success in making the combination to reach the invention as claimed.

The Examiner notes that a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. The Examiner further alleges that with regards to the dosage form or amount of a specific ingredient, one skilled in the art would be motivated to modify the different dosage forms or amounts of a specific ingredient to see which form or amount would work best in the invention as taught by the reference.

Applicants' Invention as Claimed

As noted above, the present invention, as currently amended and claimed, is directed to a pharmaceutical composition for treating a hepatic disorder and/or for increasing the number of immune cells and platelets in a patient, consisting essentially of a therapeutically effective amount of **a buffered aqueous extract** of Nigella sativa, and a pharmaceutically acceptable carrier, wherein the extract of Nigella sativa is present in a concentration of not less than 20% weight per volume.

In another embodiment, the present invention is also drawn to a pharmaceutical composition for treating a hepatic disorder and/or for increasing the number of immune cells and platelets in a patient consisting essentially of a therapeutically effective amount of **a buffered aqueous extract** of Anemone hepatica and Nigella sativa, and a pharmaceutically acceptable carrier, wherein the extract of Nigella sativa is present in a concentration of not less than 20% weight per volume. The composition may be delivered in the form of a tablet, or capsule, or liquid suspension, or may be delivered intramuscularly, subcutaneously, intravenously, intranasally, topically, transdermally, or in the form of a suppository. The composition is effective for treating patients suffering from a hepatic disorder selected from the group consisting of chronic hepatitis, advanced/late stage hepatitis, hepatitis caused by hepatitis virus genotypes I, II, II or IV, a hepatic disorder characterized by fibrosis and/or cirrhosis, a hepatic disorder resulting from an autoimmune disease and a hepatic disorder resulting from a drug treatment. Treating patients with the composition results in modification of disease activity, including but not limited to, a decrease in hepatitis viral load, and a decrease in liver enzymes alanine aminotransferase (ALT) levels and aspartate aminotransferase (AST) levels.

Applicants respectfully traverse the Examiner's rejection and as noted above, have amended the claims to better clarify what Applicants believe to be the invention. In particular, Applicants have amended claims 1 and 2 to note that the compositions consist essentially of a therapeutically effective amount **of a buffered aqueous extract** of Nigella sativa or of **a buffered aqueous extract** of Anemone hepatica and Nigella sativa, and a pharmaceutically acceptable carrier, wherein the concentration of Nigella sativa is not less than 20% weight per volume.

Applicants Position Regarding Kandil

Applicants assert that Kandil does not teach or suggest the compositions of the present invention as currently claimed. More particularly, Applicants assert that Kandil teaches away from the present invention, since Kandil uses a non-polar extract of the seeds of Nigella sativa and prepares the composition using the sterol fraction. As noted previously, Applicants respectfully draw the Examiner's attention to Figure 1 of the Kandil reference. As shown in the flow diagram, Kandil prepares the extract of Nigella sativa by crushing the seeds in a **non-polar solvent**, eg. petroleum ether or hexane, utilizes the lipid fraction (sterol fraction) and discards the non-polar solvent-insoluble components including proteins, carbohydrates, crude fiber and ash. Based on the extraction protocol outlined by Kandil in Figure 1, Applicants assert that Kandil teaches that the active moiety of Kandil is hydrophobic in nature, since Kandil discards the proteins and carbohydrates, and retains the lipid soluble fraction. On the other hand, the compositions of the present invention are prepared by soaking the seeds (not crushing them), in a polar solution, more particularly, a buffered aqueous extract is prepared by soaking the seeds from Nigella sativa in a buffered solution. Furthermore, as noted in the present application, Applicants do not prepare a lipid fraction eg. a sterol fraction, for use in the compositions of the present invention. More particularly, the claims as currently amended specifically teach a composition for treating a hepatic disorder and/or for increasing immune cell number and/or for increasing the number of platelets, consisting essentially of a buffered aqueous extract of Nigella sativa alone or in combination with an extract from Anemone hepatica, wherein the Nigella sativa extract is present in a concentration of not less than 20% weight per volume.

Applicants' Position Regarding Medenica

Applicants assert that Medenica teaches a pharmaceutical dosage form of Nigella sativa for treating cancer and for inhibiting cancer cell growth. More particularly, the Nigella sativa extract of Medenica is prepared in water or alcohol. The Examiner's attention is drawn to the paragraph in column 5, lines 20-26, whereby Medenica states that the seeds are ground in a solvent such as water or alcohol. Medenica does not teach or suggest a pharmaceutical composition for treating a hepatic disorder or for increasing immune cell number or platelet number, consisting essentially of a buffered aqueous extract of Nigella sativa alone or in combination with Anemone hepatica as taught by the present invention at a concentration of not less than 20% weight per volume. It was not until the time of the present invention that a buffered aqueous extract was used in the compositions consisting essentially of Nigella sativa alone or in combination with Anemone hepatica. Applicants assert that a composition consisting essentially of an extract of Nigella sativa, alone or in combination with an extract of Anemone hepatica, as taught by the inventors of the present application, in a buffered aqueous solution, is not taught or suggested by Medenica.

Applicants submit that it is no more than obvious to try different dosage forms or ingredients, and obvious to try has never been the proper standard for assessing obviousness. Even if, *assuming arguendo*, one of ordinary skill in the art found such dosage forms or ingredients obvious to use, the present invention is still patentable for at least the following four reasons:

1. **Neither Kandil nor Medenica teach or suggest** a pharmaceutical composition for treating a hepatic disorder or for increasing immune cell number or platelet number, consisting essentially of a therapeutically effective amount of **a buffered aqueous extract of** Nigella sativa, and a pharmaceutically acceptable carrier, wherein the extract of Nigella sativa is present **in a concentration of not less than 20% weight per volume**, as taught and currently claimed by Applicants.

2. **Neither Kandil nor Medenica teach or suggest** a composition for treating a hepatic disorder or for increasing immune cell number or platelet number, consisting essentially of a therapeutically effective amount of **a buffered aqueous extract of Anemone hepatica and**

Nigella sativa, and a pharmaceutically acceptable carrier, wherein the Nigella sativa is present **in a concentration of not less than 20% weight per volume.**

3. **Neither Kandil nor Medenica teach or suggest** a pharmaceutical composition consisting essentially **of a buffered aqueous extract of Nigella sativa alone or in combination with Anemone hepatica** for treating a hepatic disorder selected from the group consisting of chronic hepatitis, advanced stage hepatitis, hepatitis caused by hepatitis virus genotypes I, II, II or IV, a hepatic disorder characterized by fibrosis and/or cirrhosis, a hepatic disorder resulting from an autoimmune disease and a hepatic disorder resulting from a drug treatment.

4. **Neither Kandil nor Medenica teach or suggest** a pharmaceutical composition consisting essentially **of a buffered aqueous extract of Nigella sativa alone or in combination with Anemone hepatica** for treating patients suffering from late stage liver disease characterized by fibrosis and cirrhosis, wherein treating with said composition results in modification of disease activity, including but not limited to, a decrease in hepatitis viral load, and a decrease in liver enzymes alanine aminotransferase (ALT) levels and aspartate aminotransferase (AST) levels.

In summary, neither Kandil nor Medenica, when used alone or in combination, teach or suggest a pharmaceutical composition for treating a hepatic disorder or for increasing immune cell number or platelet number, wherein said composition consists essentially of **a buffered aqueous extract** of Nigella sativa alone or in combination with Anemone hepatica, and a pharmaceutically acceptable carrier, wherein the extract of Nigella sativa is present in a concentration of not less than 20% weight per volume. Moreover, there is no suggestion or motivation for treating chronic hepatitis, or late stage 4-6 (advanced stage) hepatitis patients having evidence of liver fibrosis and/or cirrhosis using the compositions of the present invention, wherein the buffered aqueous extract of Nigella sativa is present in not less than a 20% concentration, since these unexpected findings were not known until the time of the present invention. Moreover, there is no suggestion or motivation to use the compositions of the present invention for increasing the number of immune cells and platelets in patients as described by the inventors of the present application.

The present compositions provide unexpectedly superior therapeutic effects. In particular, no one to date, including Kandil or Medenica, has taught or suggested, much less demonstrated, that the compositions as claimed could be useful clinically to improve liver function and liver histopathology, as well as to enhance the immune cell number and/or function in patients at a late stage of the hepatitis disease process, particularly when fibrosis and cirrhosis are evident. To Applicants' knowledge, this is the only such therapy that is capable of improving liver function and histopathology and of reversing the liver damage observed in this patient population. Applicants assert that the Kandil and Medenica references, when used alone, or when combined, do not teach or suggest the compositions of the presently claimed invention.

Based on the foregoing, withdrawal of the rejection is respectfully requested.

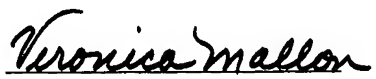
Fees

No fees are believed to be necessitated by the instant response. However, should this be in error, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment, or to credit any overpayments.

Conclusion

Applicants believe that in view of the foregoing, the claims are in condition for allowance. Withdrawal of the rejections is respectfully requested. If a discussion with the undersigned will be of assistance in resolving any remaining issues, the Examiner is invited to telephone the undersigned at (201) 487-5800, ext. 118, to effect a resolution.

Respectfully submitted,



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